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(FILE 'HOME' ENTERED AT 09:12:42 ON 27 MAR 2006)

FILE 'MEDLINE, CAPLUS, BIOSIS' ENTERED AT 09:13:00 ON 27 MAR 2006

E SIERRA HONIGMANN /AU

L1 20 S E12
L2 34279 S LEPTIN
L3 86207 S ANGIOGENESIS
L4 55034 S HEMATOPOIESIS
L5 567 S L3 (L) L4
L6 32 S L2 (L) L5
L7 16 DUP REM L6 (16 DUPLICATES REMOVED)
L8 0 S L1 (L) L7
L9 3 S L1 AND ANGIOGENESIS
L10 1 S L9 AND LEPTIN
L11 5 S L7 AND PY<2002

=> d 17 1-10 ti au so py kwic

L7 ANSWER 1 OF 16 MEDLINE on STN DUPLICATE 1
TI A role for leptin in the systemic inflammatory response syndrome (SIRS) and in immune response, an update.
AU Waelput W; Brouckaert P; Broekaert D; Tavernier J
SO Current medicinal chemistry, (2006) Vol. 13, No. 4, pp. 465-75. Ref: 175
Journal code: 9440157. ISSN: 0929-8673.
PY 2006
AB Leptin was originally identified as an adipocyte-derived cytokine with a key role in the regulation of the energy balance. Subsequent research revealed that leptin's biological action is not restricted to its effects on appetite and food intake, but instead has a much more pleiotropic character. There is now ample evidence that leptin has important functions in reproduction, hematopoiesis, HPA-axis endocrinology and angiogenesis. In this review we have focused on the effects of leptin in the antigen-specific immunity and in the inflammatory effector system.

L7 ANSWER 2 OF 16 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
TI Leptin: Structure, function and biology.
AU Zhang, Faming [Reprint Author]; Chen, Yanyun; Heiman, Mark; DiMarchi, Richard
SO Litwack, G [Editor]. Vitam. Horm. (N. Y.), (2005) pp. 345-372. Vitamins and Hormones.
Publisher: ELSEVIER ACADEMIC PRESS INC, 525 B STREET, SUITE 1900, SAN DIEGO, CA 92101-4495 USA. Series: VITAMINS AND HORMONES-ADVANCES IN RESEARCH AND APPLICATIONS.
CODEN: VIHOAQ. ISSN: 0083-6729. ISBN: 0-12-709871-2 (H).

PY 2005
AB Leptin is an adipocyte-derived hormone that acts as a major regulator for food intake and energy homeostasis. Leptin deficiency or resistance can result in profound obesity, diabetes, and infertility in humans. Since its discovery, our understanding of leptin's biological functions has expanded from antiobesity to broad effects on reproduction, hematopoiesis, angiogenesis, blood pressure, bone mass, lymphoid organ homeostasis, and T lymphocyte systems. Leptin orchestrates complex biological effects through its receptors, expressed both centrally and peripherally. Leptin receptor belongs to the class I cytokine receptor superfamily. At least five isoforms of leptin receptor exist, primarily because of alternate splicing. The longest form is capable of full signal transduction. The short forms may serve as leptin binding proteins and play a role in leptin transporting across the blood-brain barrier. In this review, we present the crystal structure of leptin and the structural comparison with other four-helical cytokines, discuss the leptin-receptor binding models based on other cytokine-receptor complex structures, and summarize the most recent progress on leptin signal transduction pathways - especially its link to peripheral lipid metabolism through AMP-activated protein kinase and hepatic stearoyl-CoA desaturase-1 pathways. Furthermore, we propose the structure based design of leptin analogs with increased stability, improved potency, enhanced blood-brain barrier transport, and extended time action for future therapeutic application. (c) 2005. . .

L7 ANSWER 3 OF 16 MEDLINE on STN
TI Leptin: structure, function and biology.
AU Zhang Faming; Chen Yanyun; Heiman Mark; Dimarchi Richard
SO Vitamins and hormones, (2005) Vol. 71, pp. 345-72. Ref: 124
Journal code: 0413601. ISSN: 0083-6729.

PY 2005
AB Leptin is an adipocyte-derived hormone that acts as a major regulator for food intake and energy homeostasis. Leptin deficiency or resistance can result in profound obesity, diabetes, and infertility in humans. Since its discovery, our understanding of leptin's biological functions has expanded from anti-obesity to broad effects on reproduction, hematopoiesis,

angiogenesis, blood pressure, bone mass, lymphoid organ homeostasis, and T lymphocyte systems. Leptin orchestrates complex biological effects through its receptors, expressed both centrally and peripherally. Leptin receptor belongs to the class I cytokine receptor superfamily. At least five isoforms of leptin receptor exist, primarily because of alternate splicing. The longest form is capable of full signal transduction. The short forms may serve as leptin binding proteins and play a role in leptin transporting across the blood-brain barrier. In this review, we present the crystal structure of leptin and the structural comparison with other four-helical cytokines, discuss the leptin-receptor binding models based on other cytokine-receptor complex structures, and summarize the most recent progress on leptin signal transduction pathways--especially its link to peripheral lipid metabolism through AMP-activated protein kinase and hepatic stearoyl-CoA desaturase-1 pathways. Furthermore, we propose the structure based design of leptin analogs with increased stability, improved potency, enhanced blood-brain barrier transport, and extended time action for future therapeutic application.

L7 ANSWER 4 OF 16 CAPLUS COPYRIGHT 2006 ACS on STN
TI The role of leptin in patients with obstructive sleep apnea syndrome
AU Harsch, Igor Alexander; Hahn, Eckhart Georg
SO Focus on Obesity Research (2005), 123-136. Editor(s): Ling, Peter R.
Publisher: Nova Science Publishers, Inc., Hauppauge, N. Y.
CODEN: 69HBUR; ISBN: 1-59454-125-6
PY 2005
AB . . . destroy sleep architecture and cause daytime sleepiness and a loss of the ability to concentrate In the OSAS patients, serum leptin levels are elevated, perhaps not only as a consequence of their typical obesity. Leptin is a hormone that is merely produced within the white adipose tissue. It plays an important role in the regulation of food intake and energy expenditure via central effects within the hypothalamus. However, leptin and leptin receptors are not only produced and expressed within the adipose tissue, but in other organs and tissues as well. Apart from the regulation of food intake and energy expenditure further effects of leptin include angiogenesis, hematopoiesis, as well as carbohydrate and lipid metabolism Furthermore, there are effects on the endocrine system, the reproductive system and development. In humans, it is not clear, whether leptin might also interfere with respiratory functions. Women, even after adjusting for body fat mass, have higher leptin levels than males and a lower incidence of OSAS. Furthermore, patients with the obstructive sleep apnea syndrome present higher leptin levels in comparison to obese controls without. Disturbances of respiratory function and leptin levels significantly decrease after nasal continuous pos. airway pressure (CPAP) treatment, irresp. of weight changes. In animal models, there is evidence for respiratory effects of leptin: Leptin-deficient and obese "ob/ob-mice" express some respiratory features that are also present in the obesity hypoventilation syndrome of humans. Such a. . . syndrome occurs, even before the mice develop their typical obesity. The respiratory symptoms can be reversed by treatment with recombinant leptin, thus, proving a central role of leptin in terms of respiratory functions in those animals. In humans, the situation concerning respiratory effects of leptin remains to be clarified, since the observed phenomena do not prove a causative mechanism and may also be epiphenomena of the conditions. Since the treatment of obese people with recombinant leptin may become a therapeutic option further information regarding a possible respiratory importance of leptin can be expected, as well as by studying the nocturnal rhythmicity of leptin in OSAS and studies in leptin-deficient persons.

L7 ANSWER 5 OF 16 MEDLINE on STN
TI Focus on leptin, a pleiotropic hormone.
AU Fietta P
SO Minerva medica, (2005 Apr) Vol. 96, No. 2, pp. 65-75.
Journal code: 0400732. ISSN: 0026-4806.
PY 2005

AB Leptin, the product of the obese gene located on human chromosome 7 (7q31.3), is a cytokine-type hormone mainly secreted by the white adipose tissue and in a lesser extent by placenta, skeletal muscle, gastric mucosa, mammary and salivary glands. Leptin, released by the adipocytes into the bloodstream in positive correlation to the fat mass, plays a key role in the. . . leptinemia rapidly falls, leading to a reduction of the energy expenditure and allowing a longer survival. Recently, pleiotropic effects of leptin have been identified, consisting in modulation of several processes, such as thermogenesis, reproduction, hemostasis, angiogenesis, hematopoiesis, osteogenesis, chondrogenesis, neuroendocrine and immune functions, as well as arterial pressure control. Leptin has been also suggested as neuroendocrinologic marker of hypervigilant state. Ultimately, it may be the signal that integrates metabolic, vascular, neuroendocrine, immune and behavioural responses. In this paper, the more recent information on leptin is reviewed and summarized.

L7 ANSWER 6 OF 16 MEDLINE on STN DUPLICATE 2
TI Serum levels of leptin in multiple myeloma patients and its relation to angiogenic and inflammatory cytokines.
AU Alexandrakis M G; Passam F H; Sfiriadaki A; Pappa C A; Moschandrea J A; Kandidakis E; Tsirakis G; Kyriakou D S
SO The International journal of biological markers, (2004 Jan-Mar) Vol. 19, No. 1, pp. 52-7.
Journal code: 8712411. ISSN: 0393-6155.

PY 2004
AB BACKGROUND: Leptin, apart from the regulation of food intake, has been implicated in hematopoiesis, the immune response and angiogenesis. Leptin has been found to be decreased in various hematological malignancies. In the present study leptin was measured in multiple myeloma (MM) patients before and after treatment and correlated with other angiogenic molecules and markers of disease activity. METHODS: Serum leptin, vascular endothelial growth factor (VEGF), basic fibroblast growth factor (b-FGF), interleukin-1 beta (IL-1beta), beta 2 microglobulin (beta2M) and C-reactive protein. . . treatment. The same parameters were measured in 20 healthy controls. Disease stage was defined according to the Durie-Salmon criteria. RESULTS: Leptin, VEGF, b-FGF, IL-1beta, and beta2M were significantly higher in newly diagnosed MM patients than in controls (p<0.05). VEGF, b-FGF, IL-1beta, beta2M, CRP but not leptin increased with advancing stage of disease (p<0.01). All parameters decreased significantly following treatment (p<0.001). Although IL-1beta correlated positively with VEGF, beta2M, b-FGF and CRP, leptin did not correlate with any of the measured parameters. CONCLUSION: Leptin serum levels do not reflect disease severity in MM. However, there seems to be a decrease in leptin following treatment, which may be associated with an alteration in the metabolic state or the chemokine milieu.

L7 ANSWER 7 OF 16 MEDLINE on STN DUPLICATE 3
TI Unraveling the multiple roles of leptin in inflammation and autoimmunity.
AU La Cava Antonio; Alviggi Carlo; Matarese Giuseppe
SO Journal of molecular medicine (Berlin, Germany), (2004 Jan) Vol. 82, No. 1, pp. 4-11. Electronic Publication: 2003-10-10. Ref: 46
Journal code: 9504370. ISSN: 0946-2716.

PY 2004
AB Initially described as an antiobesity hormone, leptin has subsequently been shown also to influence hematopoiesis, thermogenesis, reproduction, angiogenesis, and immune homeostasis. Leptin links nutritional status and proinflammatory T helper 1 immune responses, and the decrease in leptin plasma concentration during food deprivation leads to impaired immune function. This review focuses on the multiple roles of leptin in chronic inflammation and autoimmunity and suggests new possible therapeutic implications for leptin modulators.

L7 ANSWER 8 OF 16 MEDLINE on STN DUPLICATE 4
TI Appearance of leptin in wound fluid as a response to injury.
AU Marikovsky Moshe; Rosenblum Charles I; Faltin Zehava; Friedman-Einat

Miriam

SO Wound repair and regeneration : official publication of the Wound Healing Society [and] the European Tissue Repair Society, (2002 Sep-Oct) Vol. 10, No. 5, pp. 302-7.

PY Journal code: 9310939. ISSN: 1067-1927.

2002

AB The adiposity hormone **leptin** regulates food intake, body weight, reproduction and other metabolic and endocrine functions mainly through signaling to the hypothalamus. **Leptin** signaling to peripheral tissues other than the hypothalamus has been suggested for a number of processes such as immunity, bone metabolism, **hematopoiesis**, **angiogenesis**, and wound healing. It was previously shown that exogenously applied **leptin** accelerated wound healing and that **leptin** mRNA is expressed at the wound site, but there is no published evidence showing that it is translated into **leptin** protein that is available at the site of repair. To address this question we analyzed pig wound fluids collected from partial-thickness excisional wounds during the first 9 days after injury. **Leptin** was measured using a modified culture of HEK-293 cells, expressing both the human **leptin** receptor gene and the firefly luciferase gene driven by a STAT-inducible promoter. Relatively high levels of **leptin** activity (50-250 ng/ml) were detected in wound fluids using the **leptin** receptor expressing HEK-293 cells. Our results suggest that **leptin** is normally induced (4.8- to 10.2-fold) in wound tissue during the first few days following injury and may operate in. . .

L7 ANSWER 9 OF 16 MEDLINE on STN

DUPLICATE 5

TI A role for leptin in the systemic inflammatory response syndrome (SIRS) and in immune response.

AU Waelput W; Brouckaert P; Broekaert D; Tavernier J

SO Current drug targets. Inflammation and allergy, (2002 Sep) Vol. 1, No. 3, pp. 277-89. Ref: 161

Journal code: 101160019. ISSN: 1568-010X.

2002

AB **Leptin** was originally identified as an adipocyte-derived cytokine with a key role in the regulation of the energy balance. Subsequent research has, however, revealed that **leptin**'s biological action is not restricted to its effects on appetite and food intake, but rather has a much more pleiotropic character. Evidence is now accumulating that it has important functions in reproduction, **hematopoiesis**, HPA-axis endocrinology and **angiogenesis**. In this review, we have focused on the effects of **leptin** in the immune system, which can be found in both the antigen-specific immunity and in the inflammatory effector system.

L7 ANSWER 10 OF 16 MEDLINE on STN

DUPLICATE 6

TI Leptin and the treatment of obesity: its current status.

AU Lee Daniel W; Leinung Matthew C; Rozhavskaya-Arena Marina; Grasso Patricia SO European journal of pharmacology, (2002 Apr 12) Vol. 440, No. 2-3, pp. 129-39. Ref: 140

Journal code: 1254354. ISSN: 0014-2999.

2002

AB **Leptin**, the protein product of the ob gene, is primarily an adipocyte-secreted hormone, whose functional significance is rapidly expanding. Although early research efforts were focused on defining **leptin**'s role in reversing obesity in rodents, there is now substantial evidence indicating that its influence extends to several hypothalamic-pituitary-endocrine axes, including gonadal, adrenal, thyroid, growth hormone, and pancreatic islets. A role for **leptin** in **hematopoiesis**, **angiogenesis**, immune function, osteogenesis, and wound healing has also been documented. The results of recent clinical trials with recombinant human **leptin** indicated that its effectiveness in restoring energy balance and correcting obesity-related endocrinopathies in genetically obese rodent models extended only partially to the management of human obesity. New efforts in drug development have focused on **leptin**-related synthetic peptide agonists as potential anti-obesity pharmacophores.

=> d 17 11-16 ti au so py kwic

L7 ANSWER 11 OF 16 MEDLINE on STN DUPLICATE 7
TI Leptin as a novel therapeutic target for immune intervention.
AU Matarese G; Sanna V; Fontana S; Zappacosta S
SO Current drug targets. Inflammation and allergy, (2002 Mar) Vol. 1, No. 1,
pp. 13-22. Ref: 111
Journal code: 101160019. ISSN: 1568-010X.

PY 2002

AB The recent cloning of the **leptin** (obese, ob) gene has determined fundamental insight into the understanding of the regulation of food intake, basal metabolism and reproductive function. **Leptin**, mainly secreted by adipocytes, belongs to the helical cytokine family and its plasma concentrations correlate with fat mass and respond to changes in energy balance. Initially, **leptin** was considered as an anti-obesity hormone, but experimental evidence has also shown pleiotropic effects of this molecule on **hematopoiesis**, **angiogenesis**, lymphoid organ homeostasis and T lymphocyte functions. More specifically, **leptin** links the pro-inflammatory T helper (Th)-1 immune response to the nutritional status and the energy balance. Indeed, decreased **leptin** concentrations during conditions of food deprivation lead to impaired immune capabilities. This review focuses on the potential therapeutic utilities for agents that manipulate the **leptin**-adipocyte axis and discusses novel strategies for an immune intervention in pathologic conditions.

L7 ANSWER 12 OF 16 CAPLUS COPYRIGHT 2006 ACS on STN

TI Regulation of leptin production: Sympathetic nervous system interactions
AU Rayner, D. Vernon; Trayhurn, Paul
SO Journal of Molecular Medicine (Berlin, Germany) (2001), 79(1), 8-20
CODEN: JMLME8; ISSN: 0946-2716

PY 2001

AB A review with 191 refs. **Leptin** is secreted primarily from white adipose tissue and stimulates long-form OB-Rb receptors in the hypothalamus to decrease food intake and. . . the prepro-melanocortin system and cocaine- and amphetamine-regulated transcript. OB-Rb receptors (and other receptor isoforms) are also found in peripheral tissues. **Leptin** is now known to have a wide range of peripheral actions and is involved in activating the immune system, **hematopoiesis**, **angiogenesis** and as a growth factor, as well as being a regulator of many cellular functions. The identification of **leptin** has led to reappraisal of the role of white adipose tissue from being an organ concerned primarily with energy storage. . . from adipose tissue has long been known, it has become apparent that the sympathetic system is a key regulator of **leptin** production in white adipose tissue as well. Sympathomimetic amines and cold exposure or fasting (which lead to sympathetic stimulation of white fat), decrease **leptin** gene expression in the tissue and **leptin** production. On the other hand, sympathetic blockade often increases circulating **leptin** and **leptin** gene expression, and it is possible that the sympathetic system has a tonic inhibitory action on **leptin** synthesis. Apart from the few instances where **leptin** is absent, **leptin** levels are increased in obesity, while the sympathetic sensitivity of adipose tissue is reduced, consistent with the high **leptin** levels that are seen. The dysregulation of energy balance leading to obesity may partly involve a decrease in **leptin** sensitivity, or the **leptin** system may be set to have maximal effects at low **leptin** levels.

L7 ANSWER 13 OF 16 MEDLINE on STN DUPLICATE 8

TI Leptin and the pituitary.
AU Popovic V; Damjanovic S; Dieguez C; Casanueva F F
SO Pituitary, (2001 Jan-Apr) Vol. 4, No. 1-2, pp. 7-14. Ref: 48
Journal code: 9814578. ISSN: 1386-341X.

PY 2001

AB Although **leptin** was originally viewed as an antiobesity hormone, it is now evident that it may have more pleiotropic actions. Experiments in rodents have shown that **leptin** activates the sympathetic

nervous system, is involved in regulation of blood pressure, hematopoiesis, immune function, angiogenesis and brain, bone and pituitary development. Some biological effects expected based on observations in rodents, have so far not been seen in humans. Thus due to species differences in the role of leptin it is difficult to translate the data from rodents to human physiology. Hypothalamus is the primary brain site targeted by circulating leptin, secreted by fat cells. Leptin receptor has homology to members of class I cytokine receptor family, which may imply similarities in molecular events engaged by cytokines and leptin. In view of its cytokine-like properties it is likely that leptin produced and secreted outside of fat tissue i.e. in other tissues (CNS, pituitary, ovary, placenta, etc), is a paracrine regulator. Leptin receptor isoforms, long-signaling and short-nonsignaling, have been recently localized in human pituitaries. This opens the possibility of a direct action of leptin on the pituitary. However this appears to be quite complex and is species dependent. Leptin can be synthesized by normal and tumorous pituitary cells. Leptin protein expression in pituitary adenomas is decreased compared to that in normal pituitaries. Colocalization studies with leptin and anterior pituitary cells showed that 70% of ACTH cells are positive for leptin, 21% of GH cells, 29% of LH cells, 33% of FSH cells, 32% of TSH cells, 64% folliculo-stellate cells whereas very few PRL cells were positive (3%). Leptin is stored in secretory granules and secretory cells retain leptin in granules until stimulated. This follows a different secretory pathway than in adipocytes where upon synthesis leptin is immediately released. Question to be raised is does the pituitary contribute to the body leptin pool or is its action predominantly paracrine/autocrine? Clinically based evidence from studies performed in patients harboring different functional pituitary tumors. . . prolactinomas, Cushing's disease) or hypopituitarism (due to non-functioning pituitary adenomas), are in favor of a paracrine/autocrine role of the pituitary leptin. Most of the studies have shown that the link between leptin, body composition and hormones of the pituitary is indirect. Thus changes in levels of circulating leptin are most likely due to changes in the metabolic and hormonal milieu during the chronic course of the disease or chronic treatment. Furthermore, circadian rhythm of leptin, its pulsatility and gender difference are preserved in hypopituitarism as well as in patients with functional pituitary adenomas implying that intact hypothalamic-pituitary function is not essential for leptin's circadian rhythm.

L7 ANSWER 14 OF 16 MEDLINE on STN DUPLICATE 9
TI Leptin in pregnancy.
AU Henson M C; Castracane V D
SO Biology of reproduction, (2000 Nov) Vol. 63, No. 5, pp. 1219-28. Ref: 148
Journal code: 0207224. ISSN: 0006-3363.
PY 2000
AB Leptin is a polypeptide hormone that aids in the regulation of body weight and energy homeostasis and is linked to a variety of reproductive processes in both animals and humans. Thus, leptin may help regulate ovarian development and steroidogenesis and serve as either a primary signal initiating puberty or as a permissive regulator of sexual maturation. Perhaps significantly, peripheral leptin concentrations, adjusted for adiposity, are dramatically higher in females than in males throughout life. During primate pregnancy, maternal levels that arise from adipose stores and perhaps the placenta increase with advancing gestational age. Proposed physiological roles for leptin in pregnancy include the regulation of conceptus growth and development, fetal/placental angiogenesis, embryonic hematopoiesis, and hormone biosynthesis within the maternal-fetoplacental unit. The specific localization of both leptin and its receptor in the syncytiotrophoblast implies autocrine and/or paracrine relationships in this endocrinologically active tissue. Interactions of leptin with mechanisms regulating pre-eclampsia and maternal diabetes have also been suggested. Collectively, therefore, reports suggest that a better understanding of the regulation of leptin and its role(s) throughout gestation

may eventually impact those causes of human perinatal morbidity and mortality that are exacerbated by. . .

L7 ANSWER 15 OF 16 MEDLINE on STN DUPLICATE 10
TI Leptin in the regulation of immunity, inflammation, and hematopoiesis.
AU Fantuzzi G; Faggioni R
SO Journal of leukocyte biology, (2000 Oct) Vol. 68, No. 4, pp. 437-46. Ref:
135
Journal code: 8405628. ISSN: 0741-5400.
PY 2000
AB Leptin, the product of the ob gene, is a pleiotropic molecule that regulates food intake as well as metabolic and endocrine functions. Leptin also plays a regulatory role in immunity, inflammation, and hematopoiesis. Alterations in immune and inflammatory responses are present in leptin- or leptin-receptor-deficient animals, as well as during starvation and malnutrition, two conditions characterized by low levels of circulating leptin. Both leptin and its receptor share structural and functional similarities with the interleukin-6 family of cytokines. Leptin exerts proliferative and antiapoptotic activities in a variety of cell types, including T lymphocytes, leukemia cells, and hematopoietic progenitors. Leptin also affects cytokine production, the activation of monocytes/macrophages, wound healing, angiogenesis, and hematopoiesis. Moreover, leptin production is acutely increased during infection and inflammation. This review focuses on the role of leptin in the modulation of the innate immune response, inflammation, and hematopoiesis.

L7 ANSWER 16 OF 16 CAPLUS COPYRIGHT 2006 ACS on STN
TI Hypothalamic and extra-hypothalamic actions of leptin: role of leptin in the pathogenesis of obesity-related disease
AU Masuzaki, Hiroaki; Ogawa, Yoshihiro; Sato, Noriko; Yura, Shigeo; Ebihara, Ken; Abe, Megumi; Sagawa, Norimasa; Nakao, Kazuwa
SO Complication--Tonyobyo to Kekkan (1999), 4(1), 21-36
CODEN: CTKEFK; ISSN: 1342-4904
PY 1999
AB A review with 51 refs., on the title topic, discussing roles of leptin in regulation of angiogenesis, immunity, hematopoiesis, reproduction, pregnancy, and sugar and lipid metabolism and leptin formation and function in nonadipose tissues.